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(54) Title: ANTIGEN/ANTIBODY SPECIFICITY EXCHANGER

(57) Abstract

An antigen/antibody specificity exchanger is disclosed. It comprises: A) an amino-acid sequence corresponding to an amino-acid sequence of an antibody which specifically binds to a certain antigen, including hapten, B) linked by a link to C) an amino-acid sequence to which a certain antibody binds. Also, a diagnostic reagent comprising an antigen/antibody specificity exchanger according to the invention is disclosed. Said reagent may be e.g. used instead of antisera or monoclonal antibodies in *in vitro* testing systems, such as immunological tests. Further, a method of treating a disease or disorder caused by a known antigen in an individual in need of an increased number of antigen-specific antibodies is disclosed. In the method a tailor-made antigen/antibody specificity exchanger of the invention is issued. Said method may be e.g. used to redirect a patient's antibodies against poliovirus to fight HIV infection in said patient.

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ANTIGEN/ANTIBODY SPECIFICITY EXCHANGER

The present invention relates to an antigen/antibody specificity exchanger, which comprises an amino-acid sequence which specifically binds to a certain antigen linked to an amino-acid sequence to which a certain antibody binds. In vitro the antigen/antibody specificity exchanger of the invention can be used as a diagnostic reagent instead of antisera or monoclonal antibodies in testing systems, and in vivo it can be used to redirect antigens or antibodies to other antibodies or antigens, respectively, than they were originally directed to.

Background

During the past decade the antigenic structure of several viral proteins have been characterized using synthetic peptides, such as the human immunodeficiency virus-1(HIV-1)gp160, and the hepatitis B virus core/e antigens (HBc/eAg). Recently it has been shown that a synthetic peptide corresponding to the complementarity determining region 3 of the heavy chain (CDRH3) of a monoclonal antibody (mAb; F58), directed to the variable third (V3) domain of HIV-1 gp160, may act as a mini antibody and neutralize HIV-1 in vitro. In the experimental part of the present specification, the construction of synthetic peptides combining the CDRH3 domain of the mAb F58, or CDRH1, CDRH2, CDRH3 domain of Ab C1-5, and antigenic regions derived from the HIV-1 gp41, HBc/e antigen, hepatitis C virus (HCV) core protein or from the poliovirus VP1, is shown. These peptides specifically bound the V3 domain of HIV-1. Thus, it was possible to modify the antigenic surface of HIV-1 V3 peptides. This antigen/antibody specificity exchanger will be used for redirecting the reactivity of circulating antibodies and using already existing antibody specificities for a predetermined purpose. It may also serve to

alter the composition of the surface of proteins by the addition of foreign determinants. For example, the widely used poliovirus vaccination, together with the high rate of seropositivity to enteroviral proteins may be a suitable pool of antibodies to redirect against other pathogens, such as HIV.

The complementary determining regions (CDRs) of antibodies are responsible for the specificity of the antibody (1,2). X-ray crystallography has shown that the three CDRs of the variable (V) region of the heavy chain and the three CDRs of the V region of the light chain may all have contact with the epitope in an antigen-antibody complex (3). Single peptides corresponding to the CDRs of mAbs to various antigens have been shown to mimic the recognition capabilities of the respective mAb (4-10). Recently it was shown that a peptide corresponding to CDRH3 of a mAb specific for the V3 region of human immuno deficiency virus-1, holds neutralizing capacity when assayed in vitro (9). It was also observed that the CDRH2 of a mAb to hepatitis B core antigen (HBcAg) is capable of capturing HBcAg (10).

Description of the invention

The present invention is, in one aspect, directed to an antigen/antibody specificity exchanger, which comprises

A) an amino-acid sequence corresponding to an amino-acid sequence of an antibody which specifically binds to a certain antigen, including hapten,
B) linked by a link to
C) an amino-acid sequence to which a certain antibody binds.

The amino-acid sequence of A) may comprise additional amino acids or sequences on one or both sides of the amino-acid sequence of an antibody which specifically binds to a certain antigen, including hapten. Such additional amino acids and sequences may be, but are not limited to, the amino acids and sequences naturally occurring in said antibody as extensions to the amino-

acid sequence of A). The number of amino-acid residues in the amino-acid sequence of A) is preferably at least 5, and is together with possible extensions preferably less than 35.

Further, the amino-acid sequence of C) may comprise additional amino acids or sequences on one or both sides of the amino-acid sequence to which a certain antibody binds. Such additional amino acids and sequences may be, but are not limited to, the amino acids and sequences naturally occurring as extensions to the amino-acid sequence of C). The number of amino-acid residues in the amino-acid sequence of C) is preferably at least 5, and is together with possible extensions preferably less than 35.

In an embodiment of the above aspect of the invention said antigen/antibody specificity exchanger of the invention is one wherein said amino-acid sequence of A) corresponds to an amino-acid sequence of a complementarity determining region (CDR) or a framework region of a certain antibody.

In a further embodiment said antigen/antibody specificity exchanger of the invention is one wherein said amino-acid sequence of C) corresponds to an antibody-binding region of a certain protein, such as one of viral, bacterial or fungal origin.

In another embodiment said antigen/antibody specificity exchanger of the invention is one wherein said amino-acid sequence of A) is linked to said amino-acid sequence of C) by a link B), which is selected from the group consisting of a direct peptide bond and spacer molecules, such as an amino acid, an amino acid having two amino groups, linear or branched peptides or polypeptides and biotin-avidin-biotin.

In a preferred embodiment said antigen/antibody specificity exchanger of the invention is one wherein said amino-acid sequence of A) is selected from the group consisting of

SEQ ID NO: 1:
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe

SEQ ID NO: 2:
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr

SEQ ID NO: 3
Thr Tyr Ala Met Asn

SEQ ID NO: 4
Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly

and
SEQ ID NO: 5
Pro Ala Gln Gly Ile Tyr Phe Asp Tyr Gly Gly Phe Ala Tyr

In another preferred embodiment said antigen/antibody specificity exchanger of the invention is one wherein said amino-acid sequence of C) is selected form the group consisting of

SEQ ID NO: 6:
Pro Pro Asn Ala Pro Ile Leu Ser

SEQ ID NO: 7:
Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr

SEQ ID NO: 8:
Lys Glu Ile Pro Ala Leu Thr Ala Val Glu Thr Gly

SEQ ID NO: 9:
Pro Ala His Ser Lys Glu Ile Pro Ala Leu Thr Ala

SEQ ID NO: 10:
Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr

SEQ ID NO: 11:
Cys Thr Thr Ala Val Pro Trp Asn Ala Ser

and

SEQ ID NO: 12:
Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg.

Specific examples of antigen/antibody specificity exchangers of the invention:

Peptide 1:
SEQ ID NO: 13
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 2:
SEQ ID NO: 14
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr

Peptide 3:
SEQ ID NO: 15
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Lys Glu Ile Pro Ala Leu Thr Ala Val Glu Thr Gly

Peptide 4:
SEQ ID NO: 16
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Pro Ala His Ser Lys Glu Ile Pro Ala Leu Thr Ala

Peptide 5:
SEQ ID NO: 17
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Trp Gly
Cys Ser Gly Lys Leu Ile Cys Thr

Peptide 6:
SEQ ID NO: 18
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Cys Thr
Thr Ala Val Pro Trp Asn Ala Ser

Peptide 7:
SEQ ID NO: 19
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe
Lys Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe

Peptide 8:
SEQ ID NO: 20
Thr Tyr Ala Met Asn Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 9:
SEQ ID NO: 21
Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
Val Lys Gly Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 10:
SEQ ID NO: 22
Pro Ala Gln Gly Ile Tyr Phe Asp Tyr Gly Gly Phe Ala Tyr Pro Pro
Asn Ala Pro Ile Leu Ser

Peptide 11:
SEQ ID NO: 23
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Gln Arg Lys
Thr Lys Arg Asn Thr Asn Arg Arg

Another aspect of the invention is directed to a diagnostic reagent comprising an antigen/antibody specificity exchanger according to the invention.

Such a diagnostic reagent of the invention may be used to detect in vitro specific antigens in biological samples, e.g. body fluid or tissue samples. Thus, the diagnostic reagent of the invention may be used instead of antisera or monoclonal antibodies in in vitro testing systems, such as immunological tests, e.g. Enzyme-Linked Immunosorbent Assay (ELISA), Enzyme Immunoassay (EIA), Western Blot, Radioimmunoassay (RIA) etc. Further, the diagnostic reagent of the invention may be used to investigate biological properties of biological systems.

Still another aspect of the invention is directed to a method of treating a disease or disorder caused by a known antigen in an individual in need of an increased number of antigen-specific antibodies, which comprises administration to said individual of a sufficient amount of a tailor-made antigen/antibody specificity exchanger according to the invention which binds to certain antibodies known to exist in said individual.

An individual in need of an increased number of antigen-specific antibodies against a known antigen, which causes a disease or disorder in said individual, may be one who will benefit from getting a rapid increase in the number of such antigen-specific antibodies, or who even lacks or has insufficient ability to elicit antibodies against said known antigen. Said individual may be a human or non-human mammal.

Such a tailor-made antigen/antibody specificity exhanger according to the invention is designed so that certain antibodies existing in the patient in question, (e.g. antibodies against viral proteins, such as antibodies against poliovirus, antibodies against virus causing measles, antibodies against hepatitis B virus, antibodies against hepatitis C virus, antibodies against HIV-1, whether induced by natural infection or vaccination) binds to the amino-acid sequence of C) and the amino-acid sequence of A) binds to a known antigen causing a disease or disorder in said patient (e.g. HIV).

Thus, existing antibodies in said patent are redirected to said known antigen (against which said patient e.g. lacks or has insufficient amount of desired antibodies).

A specific example of an antigen/antibody specificity exchanger of the invention is a peptide which binds to antibodies against poliovirus and also binds specifically to HIV virus. Thus, already high titres in a patient of antibodies against poliovirus may thus be used to fight HIV infection in said patient.

Preparation of the antigen/antibody specificity exchanger of the invention

The antigen/antibody specificity exchanger of the invention is prepared in any suitable manner known in the art. It is in most cases a peptide, with the exception of the case when it comprises biotin-avidin-biotin as a linker. As is well-know in the art, peptides can be produced by genetic engineering methods or peptide synthesis. In peptide synthesis one amino-acid residue is coupled to the next one in liquid phase, or starting with the solid phase to which the C-terminal of the first amino acid is coupled, whereupon the C-terminal of the next amino acid is coupled to the N-terminal of the first amino acid, etc, finally releasing the build-up peptide from the solid phase.

The antigen/antibody specificity exchangers presented in Table 1 are all synthetic peptides synthesized according to a method for multiple peptide synthesis (21) and by a Milligen 9050 peptide synthesizer using 9-fluorenylmethoxy-carbonyl-protected amino acid esters (20). All peptides were analysed and/or purified by reverse phase HPLC using a Pep-S 5m column (Pharmacia-LKB, Uppsala, Sweden), run with a gradient from 10% to 60% CH3CN against water containing 0.1% trifluoro-acetic acid.

Testing of the antigen/antibody specificity exchanger of the invention

Monoclonal antibodies and human sera. The production and characterization of mAb to HBc/eAg has been described (15, 18). The mAb 14E11 recognizes the epitope at residues 135-141 (PNAPILS), of the HBc/eAg sequence (15). The monoclonal antibody 14E11 was kindly provided by Dr. Alexander Cimanis, Riga. Two human sera (A and B) reactive to a peptide covering residues 42-55 of VP1 of poliovirus 1 have previously been described (19). A monoclonal antibody against enteroviral VP1 was purchased from Dako (CBV; M7064, Dako, Copenhagen, Denmark)

Three human sera (C, D and E) positive for antibodies to hepatitis C virus (HCV) core residues 7-19 have previously been described (20).

Enzyme immuno assays (EIAs). Strain-specific HIV-1 V3 peptides were coated on microtiter wells (Nunc 96F Certificated; Nunc, Copenhagen, Denmark) in 100 ml portions at concentrations of from 10 mg/ml to 0.01 mg/ml in 0.05 M sodium carbonate buffer, pH 9.6, at +4°C overnight. Excess peptides were removed by washing with PBS containing 0.05% Tween 20.
The peptide-coated plates were assayed for binding using the peptides of the invention diluted from 100 mg/ml to 0.01 mg/ml in PBS containing 1% BSA, 2% goat serum, and 0.05% Tween 20. The dilutions of the peptides of the invention were added in 100 ml

portions and incubated with the adsorbed V3 peptides for 60 minutes at +37°C. Excess test peptides were removed by washing and bound peptide was indicated by the respective mAb or anti-serum, by incubation for 60 minutes at +37°C. The amount of bound antibody was indicated by an additional incubation of enzyme-labelled secondary antibody, rabbit anti-mouse Ig (P260, Dako, Copenhagen, Denmark) for mAbs, and goat anti-human IgG (A-3150; Sigma Chemicals, St. Louis, MO) for human antibodies. The amount of bound conjugate was determined by addition of substrate and the absorbances were measured at 492 nm or 405 nm in a spectrophoto-meter.

Antibody recognition of peptides of the invention. When adsorbed to microplates all peptides of the invention presented in Table 1 except for Nos. 4 (Table 2) and 7 (data not shown) were found to be reactive with the respective antibodies.

Antigen binding of the peptides of the invention. The antigenically functional test peptides were further evaluated for binding of HIV-1 V3 peptide, MN-strain. All test peptides which had a functional antigenic region were found to directly bind to the HIV-1 V3 peptide (Tables 3 and 4). As shown in Tables 3 and 4, the reactivity to the HIV-1 V3 peptide was found to be dependent on both concentrations of the test peptides and of V3 peptides, indicating a specific reactivity. This clearly indicates that it was possible to redirect antibodies specific for HIV-1 gp41, HBc/eAg and poliovirus 1 VP1 to bind to the altered antigenic surface of the HIV-1 V3 peptide. It was also found, that pre-incubation of equimolar concentrations of mAb 14E11 and the corresponding test peptide of the invention, did not change the ability of the test peptide mAb complex to bind to the V3 peptide (data not shown). This indicates that it is possible to add antigenic domains to a CDR peptide with retained antigen binding ability of the CDR sequence.

The ability of the antigen/antibody specificity exchangers to redirect antibodies was further evaluated in a system where the CDRH1, CDRH2 and CDRH3 sequences from mAb C1-5 were added to the epitope sequence for mAb 14E11. A peptide corresponding to the epitope sequence for mAb C1-5, residues 71-90 of HBc/eAg with an Ile at position 80, was adsorbed to microplates. The antigen/-antibody specificity exchangers, based on the C1-5 CDRs, were then added, and the amount bound CDR peptide was indicated by the epitope specific mAb 14E11. The results clearly showed that the mAb 14E11 which originally recognized residues 134-141 of the HBc/eAg sequence was redirected by the antigen/antibody specificity exhanger containing the CDRH2 sequence (Table 5). Also, this reactivity was dependent on the amount CDR added, indicating a specific reaction ($p<0.01$, Regression analysis; Table 5).

Further, in Table 7 is shown that the antigen/antibody specificity exchanger of the invention can redirect an existing HBc/eAg specific antibody to significantly bind to HIV-1 V3 peptides of several different subtypes.

Thus, it is evident that the antigen/antibody exchanger of the invention forms the basis of a novel method for redirecting the specificity of monoclonal and polyclonal antibodies by modifying the antigenic surface of a viral protein.

It should be understood that the invention comprises antigen/antibody exchangers wherein included amino-acid sequences are chemically stabilized e.g. by cyclization and wherein included amino-acid sequences may have specific amino-acid deletions, additions and/or substitutions. Such modified amino-acid sequences may result in antigen/antibody exchangers exhibiting increased (or decreased) biological activities.

Table. 1. Antigen/antibody specificity exchangers of the invention represented by peptides containing the CDRH3 domain of mAb F58 or CDRH1, CDRH2, CDRH3 domain of mAb C1-5 (A) and different antigenic regions derived from viral proteins (C).

Peptide No.	Amino-acid sequence (A)	link (B)	Amino-acid sequence (C)	Source of aas (C)	Ref.
1.	SEQ ID N0 1.	peptide bond	SEQ ID NO 6	HBc/eAg, aas 134-141	15
2.	SEQ ID NO 1.	peptide bond	SEQ ID NO 7	HBc/eAg, aas 133-142	15
3.	SEQ ID NO 1.	peptide bond	SEQ ID NO 8	Polio VP1, aas 39-50	16
4.	SEQ ID NO 1.	peptide bond	SEQ ID NO 9	Polio VP1, aas 35-46	16
5.	SEQ ID NO 1.	peptide bond	SEQ ID NO 10	HIV-1 gp41, aas 596-605	20
6.	SEQ ID NO 1.	peptide bond	SEQ ID NO 11	HIV-1 gp41 aas 603-612	20
7.	2(SEQ ID NO 1)	Lys	SEQ ID NO 7	HBc/eAg, ass 133-142	15
8.	SEQ ID NO 3.	peptide bond	SEQ ID NO 6	HBc/eAg, aas 134-141	15
9.	SEQ ID NO 4.	peptide bond	SEQ ID NO 6	HBc/eAg, aas 134-141	15
10.	SEQ ID NO 5.	peptide bond	SEQ ID NO 6	HBc/eAg, aas 134-141	15
11.	SEQ ID NO 2.	peptide bond	SEQ ID NO 12	HCV core 8-18	22

Note: aas = amino acids

Table 2. Testing of antigen/antibody specificity exchanger of the invention represented by peptides passively adsorbed to polystyrene for ability to be recognized by antibodies specific for the antigenic region presented in the peptide. Values are given as the absorbance obtained at 492 or 405 nm.

Peptide No.	Antibody used	Amount peptide added (ng/0.1 ml) to solid phase 1.000	100	10	1	0.1	0.01
1	14E11	2.500	1.675	0.030	0.010	0.009	0.008
2	14E11	2.500	1.790	0.008	0.006	0.008	0.006
3	CBV	2.500	1.142	0.036	0.020	0.019	0.036
	human A	1.945	1.850	0.486	0.088	0.115	0.116
	human B	1.342	0.770	0.130	0.065	0.090	0.095
4	CBV	0.020	0.018	0.015	0.016	0.017	0.018
	human A	0.059	0.081	0.108	0.109	0.097	0.100
	human B	0.052	0.072	0.091	0.098	0.083	0.100

Note: Regression analysis of the relation between absorbance and peptide concentration gives $p<0.01$.

Table 3. Testing of the HIV-1 V3 peptide-antigen binding capability of the CDR sequence simultaneously with the ability to be recognized by monoclonal antibodies specific for the antigenic region on the test peptide of the invention. Values are given as the absorbance at 492 nm.

a:

Peptide No.	Anti-body used	Amount of test peptide (ng/0.1 ml)	Amount V3 peptide added (ng/0.1 ml) to solid phase 1.000	500	250	125	62.5	31.25
1	14E11	10,000	2.500	2.500	2.500	2.338	1.702	1.198
		5,000	2.500	2.500	2.500	2.190	1.622	1.122
		2,500	2.500	2.500	2.500	2.039	1.394	0.990
		1,250	2.500	2.500	2.500	1.712	0.930	0.771
		625	1.936	0.824	0.380	0.152	0.056	0.053
		312	0.196	0.085	0.044	0.043	0.030	0.025

Note: Regression analysis of the relation between absorbance and CDR peptide concentration, and relation between absorbance and V3 peptide concentration gives $p<0.01$, respectively.

b:

Peptide No.	Anti-body used	Amount of test peptide (ng/0.1 ml)	Amount of V3 peptide added (ng/0.1 ml)					
			1.000	500	250	125	62.5	31.25
4	14E11	10.000	2.500	2.500	2.133	1.560	1.070	0.829
		5.000	2.500	2.500	1.963	1.645	1.074	0.981
		2.500	2.500	2.500	1.729	1.404	0.962	0.747
		1.250	2.500	2.424	1.433	1.327	0.795	0.488
		625	0.835	0.359	0.200	0.120	0.088	0.073
		312	0.099	0.054	0.042	0.049	0.045	0.025

c:

Peptide No.	Anti-body used	Amount of test peptide (ng/0.1 ml)	Amount peptide added (ng/0.1 ml) to solid phase					
			1.000	100	10	1	0.1	0.01
3	CBV	10,000	0.523	0.498	0.162	0.161	0.017	0.017
		1,000	0.053	0.054	0.031	0.027	0.010	0.010
		100	0.034	0.037	0.025	0.029	0.010	0.010
		10	0.023	0.022	0.014	0.014	0.010	0.009
		1	0.013	0.044	0.014	0.017	0.027	0.009
		0.1	0.011	0.009	0.008	0.032	0.013	0.013

Note: Regression analysis of the relation between absorbance and CDR peptide concentration, and relation between absorbance and V3 peptide concentration gives $p<0.01$, respectively.

Table 4. Testing of the HIV-1 V3 peptide antigen binding capability of the CDR sequence simultaneously with the ability to be recognized by human anti-polio VP1 polyclonal antibodies specific for the antigenic region on the test peptides of the invention. Values are given as the absorbance at 405 nm.

a:

Peptide No.	Anti-body used	Amount of test peptide (ng/0.1 ml)	Amount V3 peptide added to solid phase (ng/0.1 ml) 1.000	500	250	125	62.5	31.25
3	human A	10,000	1.538	1.356	1.448	1.052	0.280	0.123
		5,000	1.179	1.050	1.006	0.557	0.136	0.087
		2,500	0.684	0.558	0.604	0.216	0.084	0.067
		1,250	0.367	0.358	0.332	0.162	0.075	0.062
		625	0.228	0.238	0.220	0.121	0.083	0.063
		312	0.171	0.154	0.154	0.103	0.072	0.060

Note: Regression analysis of the relation between absorbance and CDR peptide concentration, and relation between absorbance and V3 peptide concentration gives $p<0.01$, respectively.

Table 4, continued.

b:

Peptide No.	Anti-body used	Amount of test peptide (ng/0.1 ml)	Amount V3 peptide added to solid phase (ng/0.1 ml) 1.000	500	250	125	62.5	31.25
3	human B	10,000	0.366	0.352	0.352	0.200	0.074	0.056
		5,000	0.206	0.217	0.188	0.131	0.063	0.053
		2,500	0.134	0.132	0.126	0.091	0.061	0.055
		1,250	0.107	0.114	0.108	0.077	0.060	0.054
		625	0.082	0.104	0.087	0.075	0.063	0.056
		312	0.083	0.091	0.094	0.077	0.068	0.060

Note: Regression analysis of the relation between absorbance and CDR peptide concentration, and relation between absorbance and V3 peptide concentration gives $p<0.01$, respectively.

Table 5. Testing of the HIV-1 V3 peptide antigen capability of the CDR sequence simultaneous with the ability to be recognized by human anti-HCV core polyclonal antibodies specific for the antigenic region on the test peptides of the invention. Values are given as the absorbance at 405 nm.

Peptide No.	Antibody used	Amount of V3 pepitide (ng/0.1 ml)	Amount of test peptide added (ng/0.1 ml)					
			62	31	15	7.5	3.7	1.8
11	human HCV-C	625	2.500	2.416	2.097	1.473	0.973	0.630
		78	2.500	2.335	1.781	1.225	0.825	0.564
		39	2.389	2.287	1.626	1.081	0.664	0.389
11	human HCV-D	625	1.999	1.490	1.184	0.751	0.458	0.428
		78	1.758	1.370	1.025	0.612	0.468	0.380
		39	1.643	0.993	0.833	0.497	0.343	0.287
11	human HCV-E	625	2.368	2.165	1.656	1.104	0.645	0.462
		78	2.156	1.824	1.396	0.733	0.514	0.352
		39	1.893	1.683	1.110	0.756	0.310	0.272

Table 6. Testing of C1-5 CDRs(10ug/ml) (in test peptides of the invention) with a peptide corresponding to HBc/eAg corresponding to residues 71-90) coated on solid phase. Bound CDR was indicated by the epitope specific mAb 14E11.

CDR sequence	Anti-body used	Amount c71-90 peptide (ng/0.1 ml)	Amount of test peptide added (ng/0.1ml)					
			10.000	5.000	2.500	1.250	625	312
Peptide 8:	14E11	625	0.003	0.002	0.002	0.002	0.002	0.002
CDRH1		312	0.002	0.002	0.004	0.003	0.006	0.004
(SEQ ID NO3)		78	0.003	0.003	0.005	0.005	0.003	0.003
Peptide 9:	14E11	625	2.500	1.303	0.070	0.012	0.003	0.002
CDRH2		312	2.500	1.070	0.058	0.011	0.003	0.002
(SEQ ID NO4)		78	2.500	0.868	0.039	0.008	0.003	0.003
Peptide 10:	14E11	625	0.004	0.003	0.004	0.003	0.003	0.003
CDRH3		312	0.004	0.003	0.004	0.004	0.003	0.003
(SEQ ID NO5)		78	0.005	0.004	0.005	0.005	0.004	0.004

Table 7. Redirecting existing HBc/eAg specific antibody (14E11, from Dr. A. Tsimanis, Riga) to different subtype-specific HIV-1 V3 peptides (subtypes A-E) via specificity exchanger peptide containing CDRH3 sequence against HIV-1 and a HBc/eAg epitope for mAb 14E11.

HIV-1 V3 peptide attached to solid-phase	Reactivity (absorbance at 405 nm) of specificity exchanger peptide added in the indicated amount (ng)					
	500	250	125	62.5	31.25	15.625
Subtype A	0.378	0.126	0.078	0.068	0.062	0.017
Subtype B	2.686	2.536	1.710	1.329	0.360	0.157
Subtype C	1.261	0.514	0.111	0.077	0.051	0.020
Subtype D	0.17	0.079	0.065	0.028	0.029	0.026
Subtype E	0.22	0.090	0.093	0.032	0.063	0.030

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Ferring AB
(B) STREET: Box 30047
(C) CITY: Malmo
(E) COUNTRY: Sweden
(F) POSTAL CODE (ZIP): S-200 61
(G) TELEPHONE: 040-361000
(H) TELEFAX: 040-154795

(ii) TITLE OF INVENTION: Antigen/antibody specificity exchanger

(iii) NUMBER OF SEQUENCES: 23

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr
1 5 10

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Thr Tyr Ala Met Asn
1 5

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Pro Ala Gln Gly Ile Tyr Phe Asp Tyr Gly Gly Phe Ala Tyr
1 5 10

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Pro Pro Asn Ala Pro Ile Leu Ser
1 5

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Lys Glu Ile Pro Ala Leu Thr Ala Val Glu Thr Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Pro Ala His Ser Lys Glu Ile Pro Ala Leu Thr Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Cys Thr Thr Ala Val Pro Trp Asn Ala Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Pro Pro
1 5 10 15

Asn Ala Pro Ile Leu Ser
20

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Arg Pro
1 5 10 15

Pro Asn Ala Pro Ile Leu Ser Thr
20

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Lys Glu
1 5 10 15

Ile Pro Ala Leu Thr Ala Val Glu Thr Gly
20 25

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Pro Ala
1 5 10 15

His Ser Lys Glu Ile Pro Ala Leu Thr Ala
20 25

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Trp Gly
1 5 10 15

Cys Ser Gly Lys Leu Ile Cys Thr
20

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Cys Thr
1 5 10 15

Thr Ala Val Pro Trp Asn Ala Ser
20

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(D) OTHER INFORMATION: /label= SEQIDNO19
/note= ""Lys in position 15 is substituted by SEQ ID NO 1""

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Lys Arg
1 5 10 15

Pro Pro Asn Ala Pro Ile Leu Ser Thr
20 25

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Thr Tyr Ala Met Asn Pro Pro Asn Ala Pro Ile Leu Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly Pro Pro Asn Ala Pro Ile Leu Ser
20 25

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Pro Ala Gln Gly Ile Tyr Phe Asp Tyr Gly Gly Phe Ala Tyr Pro Pro
1 5 10 15

Asn Ala Pro Ile Leu Ser
20

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Gln Arg Lys
1 5 10 15

Thr Lys Arg Asn Thr Asn Arg Arg
20

CLAIMS

1. Antigen/antibody specificity exchanger, characterised in that it comprises
A) an amino-acid sequence corresponding to an amino-acid sequence of an antibody which specifically binds to a certain antigen, including hapten,
B) linked by a link to
C) an amino-acid sequence to which a certain antibody binds.

2. Antigen/antibody specificity exchanger according to claim 1, wherein said amino-acid sequence of A) corresponds to an amino-acid sequence of a complementarity determining region (CDR) of a certain antibody.

3. Antigen/antibody specificity exchanger according to claim 1, wherein said amino-acid sequence of C) corresponds to an antibody-binding region of a certain protein.

4. Antigen/antibody specificity exchanger according to claim 1, wherein said amino-acid sequence of A) is linked to said amino-acid sequence of C) by a link B), which is selected from the group consisting of a direct peptide bond and spacer molecules.

5. Antigen/antibody specificity exchanger according to claim 2, wherein said amino-acid sequence of A) is selected from

SEQ ID NO: 1:
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe

SEQ ID NO: 2:
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr

SEQ ID NO: 3
Thr Tyr Ala Met Asn

SEQ ID NO: 4
Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly

and

SEQ ID NO: 5
Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly

6. Antigen/antibody specificity exchanger according to claim 3, wherein said certain protein is of viral, bacterial or fungal origin.

7. Antigen/antibody specificity exchanger according to claim 6, wherein said amino-acid sequence of C) is selected form the group consisting of

SEQ ID NO: 6:

Pro Pro Asn Ala Pro Ile Leu Ser

SEQ ID NO: 7:

Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr

SEQ ID NO: 8:

Lys Glu Ile Pro Ala Leu Thr Ala Val Glu Thr Gly

SEQ ID NO: 9:

Pro Ala His Ser Lys Glu Ile Pro Ala Leu Thr Ala

SEQ ID NO: 10:

Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr

SEQ ID NO: 11:

Cys Thr Thr Ala Val Pro Trp Asn Ala Ser

and

SEQ ID NO: 12:

Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg.

8. Antigen/antibody specificity exchanger according to claim 1, wherein it is selected from the group consisting of

Peptide 1:
SEQ ID NO: 13
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 2:
SEQ ID NO: 14
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr

Peptide 3:
SEQ ID NO: 15
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Lys Glu Ile Pro Ala Leu Thr Ala Val Glu Thr Gly

Peptide 4:
SEQ ID NO: 16
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Pro Ala His Ser Lys Glu Ile Pro Ala Leu Thr Ala

Peptide 5:
SEQ ID NO: 17
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr

Peptide 6:
SEQ ID NO: 18
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe Cys Thr Thr Ala Val Pro Trp Asn Ala Ser

Peptide 7:
SEQ ID NO: 19
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe

Lys Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr

Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Phe

Peptide 8:
SEQ ID NO: 20
Thr Tyr Ala Met Asn Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 9:
SEQ ID NO: 21
Arg Val Arg Ser Lys Ser Phe Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 10:
SEQ ID NO: 22
Pro Ala Gln Gly Ile Tyr Phe Asp Tyr Gly Gly Phe Ala Tyr Pro Pro Asn Ala Pro Ile Leu Ser

Peptide 11:
SEQ ID NO: 23
Cys Asp Leu Ile Tyr Tyr Asp Tyr Glu Glu Asp Tyr Tyr Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg.

9. Antigen/antibody specificity exchanger according to claim 4, wherein said spacer molecules are selected from an amino acid, an amino acid having two amino groups, linear or branched peptides, polypeptides and biotin-avidin-biotin.

10. Diagnostic reagent comprising an antigen/antibody specificity exchanger according to any one of claims 1-9.

11. A method of treating a disease or disorder caused by a known antigen in an individual in need of an increased number of antigen-specific antibodies, which comprises administration to said individual of a sufficient amount of a tailor-made antigen/antibody specificity exchanger according to claim 1 which binds to certain antibodies known to exist in said individual.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00468

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 16/00, C07K 19/00, A61K 39/395, G01N 33/05, C12N 15/13
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K, A61K, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5196510 A (JOHN D. RODWELL ET AL), 23 March 1993 (23.03.93), see column 18-28 and claims --	1-4,6,9,10
X	US 5091513 A (JAMES S. HUSTON ET AL), 25 February 1992 (25.02.92), column 2 - column 3 --	1-4,6,9,10
X	National Library of Medicine, file Medline, Medline accession no. 93380831, Bianchi E: "Affinity purification of a difficult-sequence protein. Implications for the inclusion of capping in synthetic protocols", Int J Pept Protein Res 1993 Jul;42(1):93-6 --	1-4,6,9,10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 1995	29.08.95
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carl Olof Gustafsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00468

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	National Library of Medicine, file Medline, Medline accession no. 93266348, Bianchi E: "Chemical synthesis of a disigned beta-protein through the flow-polyamide method", Int J Pept Protein Res 1993 Apr;41(4):385-93	1-4,6
A	Dialog Information Services, file 55, Biosis, Dialog accession No. 11257821, Biosis accession No. 97457821, Tramontano A. et al: "The making of the minibody: An engineered beta-protein for the display of conformationally constrained peptides", Journal of Molecular Recognition 7 (1). 1994. 9-24	1-4,6,9,10
X	Proc.Natl.Acad.Sci., Volume 90, July 1993, Philipp Holliger et al, ""Diabodies": Small bivalent and bispecific antibody fragments", page 6444 - page 6448, see"Discussion"	1-4,6,9,10
X	WO 9315210 A1 (MERCK PATENT GMBH), 5 August 1993 (05.08.93), page 8 - page 9; page 14	1-4,6,9,10
A	Proc.Natl.Acad.Sci., Volume 90, May 1993, Michael Levi et al, "A complementarity-determining region synthetic peptide acts as a miniantibody and neutralizes human immunodeficiency virus type 1 in vitro" page 4374 - page 4378	5,7
A	Science, Volume 253, 1991, Horacio Uri Saragovi et al, "Design and Synthesis of a Mimetic from an Antibody Complementarity-Determining Region" page 792 - page 795	1-4
A	Nature, Volume 355, January 1992, Maurizio Zanetti, "Antigenized antibodies" page 476 - page 477	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00468

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0182546 A2 (POLYCLONAL ANTIBODIES LIMITED), 28 May 1986 (28.05.86) --	1-4,6,9,10
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